

EXHIBIT A: PENDING CLAIMS
U.S. PATENT APPLICATION SERIAL NO. to be assigned
(ATTORNEY DOCKET NO. 9301-129)

(As amended February 14, 2001)

1. A method of determining a level of one or more disease states in a subject, said method comprising determining, for each of said disease states, an interpolated response profile, from interpolated perturbation response profiles correlated to levels of each of said disease states, for which similarity is greatest between a diagnostic profile and said one or a combination of said determined interpolated response profiles, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response profiles are the products of a method comprising

- (i) providing response profiles of one or more cells of one or more analogous subjects for each of said disease states wherein said response profiles are obtained by measuring a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels for each of said disease states, and
- (ii) interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said disease states,

wherein the level of each disease state correlated to each determined interpolated response profile indicates said levels of said disease states.

57. (New) A method for diagnosing a subject having a disease, said method comprising

(1) determining a level of said disease state in said subject by a method comprising determining, for said disease state, an interpolated response profile, extracted from interpolated response curves correlated to level of said disease state, for which similarity is greatest between a diagnostic profile and said determined interpolated response profile, said diagnostic profile comprising measured amounts of a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response curves are the products of a method comprising

- (i) providing response profiles of one or more cells of one or more analogous subjects for said disease state wherein said response profiles comprise

measured amounts of a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels of said disease state, said second plurality comprising at least a portion of said first plurality, and

- (ii) interpolating said response profiles so that a response profile may be extracted over a range of levels of said disease states,

wherein the level of disease state correlated to said determined interpolated response profile indicates said level of said disease state;

- (2) determining statistical significance of said level of said disease state; and

(3) diagnosing said patient if said statistical significance of said level of said disease state is at least 95%.

58. (New) The method of claim 57, wherein said interpolated response profile yields a maximum correlation between said diagnostic profile and said interpolated response profile.

59. (New) The method of claim 58, wherein said statistical significance of said level of said disease state is determined by comparing the value of said maximum correlation to an expected probability distribution of values of maximum correlation.

60. (New) The method of claim 59, wherein said expected probability distribution of values of maximum correlation is obtained by a method comprising

(1) randomizing said diagnostic profile data with respect to cellular constituents to generate a permuted diagnostic profile;

(2) obtaining an interpolated response profile, said interpolated response profile yielding a maximum correlation between said permuted diagnostic profile and said interpolated response profile; and

(3) repeating steps (1) and (2) to construct a probability distribution of values of maximum correlation.

61. (New) The method of claim 59, wherein said expected probability distribution of values of maximum correlation is obtained by a method comprising

(1) randomizing said response profile data with respect to the cellular constituents to generate permuted interpolated response curves;

(2) obtaining an interpolated response profile, said interpolated response profile being extracted from said permuted interpolated response curves and yielding a maximum correlation between said diagnostic profile and said interpolated response profile; and

(3) repeating steps (1) and (2) to construct a probability distribution of values of maximum correlation.

62. (New) The method of claim 57, wherein said interpolated response profile yields a minimum difference between said diagnostic profile and said interpolated response profile.

63. (New) The method of claim 62, wherein said statistical significance of said level of said disease state is determined by comparing the value of the minimum difference to an expected probability distribution of values of minimum difference.

64. (New) The method of claim 63, wherein said expected probability distribution of values of minimum difference is obtained by a method comprising

(1) randomizing said diagnostic profile data with respect to the cellular constituents to generate a permuted diagnostic profile;

(2) obtaining an interpolated response profile, said interpolated response profile yielding a minimum difference between said permuted diagnostic profile and said interpolated response profile; and

(3) repeating steps (1) and (2) to construct a probability distribution of values of minimum difference.

65. (New) The method of claim 63, wherein said expected probability distribution of values of minimum difference is obtained by a method comprising

(1) randomizing said response profile data with respect to the cellular constituents to generate permuted interpolated response curves;

(2) obtaining an interpolated response profile, said interpolated response profile being extracted from said permuted interpolated response curves and yielding a minimum difference between said diagnostic profile and said interpolated response profile; and

(3) repeating steps (1) and (2) to construct a probability distribution of values of minimum difference.

66. (New) A method for determining statistical significance of a determined level of a disease state in a subject, said method comprising

(1) providing a diagnostic profile comprising measured amounts of a first plurality of cellular constituents in one or more cells of said subject;

(2) providing response profiles of one or more cells of one or more analogous subjects for said disease state wherein said response profiles comprise measured amounts of a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels of said disease state, said second plurality comprising at least a portion of said first plurality;

(3) obtaining interpolated response curves by interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said disease states;

(4) determining said level of said disease state by a method comprising minimizing value of an objective function of the difference between said diagnostic profile and said interpolated response curves; and

(5) determining statistical significance of said level of said disease state.

67. (New) A method for determining statistical significance of a determined level of an effect of a therapy upon a subject, said method comprising

(1) providing a diagnostic profile comprising measured amounts of a first plurality of cellular constituents in one or more cells of said subject;

(2) providing response profiles of one or more cells of one or more analogous subjects for said therapy wherein said response profiles comprise measured amounts of a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels of effect for said therapy, said second plurality comprising at least a portion of said first plurality;

(3) obtaining interpolated response curves by interpolating said response profiles so that a response profile may be extracted over a range of levels for each of said effect for said therapy;

(4) determining said level of said effect of said therapy by a method comprising minimizing value of an objective function of the difference between said diagnostic profile and said interpolated response curves; and

(5) determining statistical significance of said level of said effect of said therapy.

68. (New) A computer system for diagnosing a subject having a disease comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising

(1) determining, for said disease state, an interpolated response profile, extracted from interpolated response curves correlated to level of said disease state, for which similarity is greatest between a diagnostic profile and said determined interpolated response profile, said diagnostic profile comprising measured amounts of a first plurality of cellular constituents in one or more cells of said subject, and wherein said interpolated response curves are the products of a method comprising

(i) providing response profiles of one or more cells of one or more analogous subjects for said disease state wherein said response profiles comprise measured amounts of a second plurality of cellular constituents in said cells of said one or more analogous subjects at a plurality of levels for said disease state, said second plurality comprising at least a portion of said first plurality, and

(ii) interpolating said response profiles so that a response profile may be extracted over a range of levels for said disease state,

wherein the level of disease state correlated to said determined interpolated response profile indicates said level of said disease state;

(2) determining statistical significance of said level of said disease state; and

(3) indicating a diagnosis that said subject has said disease at said level if said statistical significance of said level of disease state is at least 95%.

69. (New) The computer system of claim 68 wherein said step of determining said interpolated response profile is achieved by a method comprising:

(a) determining a value of an objective function of the difference between said diagnostic profile and said interpolated response curves; and

- (b) minimizing said determined value of said objective function.

70. (New) The computer system of claim 69, wherein said statistical significance of said level of said disease state is determined by comparing said determined minimum value to an expected probability distribution of minimum values.

71. (New) The computer system of claim 68 wherein said step of determining said interpolated response profile is achieved by a method comprising:

- (a) determining a value of an objective function of the correlation between said diagnostic profile and said interpolated response curves; and
- (b) maximizing said determined value of said objective function.

72. (New) The computer system of claim 71, wherein said statistical significance of said level of said disease state is determined by comparing said determined maximum value to an expected probability distribution of maximum values.

73. (New) The computer system of claim 68 wherein said diagnostic profile and said response curves are made available in said memory.

74. (New) The computer system of claim 68 wherein said programs cause said processor to perform said step of interpolating said response profiles.

75. (New) The computer system of claim 69 or 70 wherein said objective function comprises a sum of the squares of differences of said diagnostic profile and said interpolated response profile.